

University of Groningen

## Inhibitor development in previously untreated patients with severe haemophilia

Jonker, Carla J.; Oude Rengerink, Katrien; Hoes, Arno W.; Mol, Peter G. M.; van den Berg, H. Marijke

*Published in:*  
Haemophilia

*DOI:*  
[10.1111/hae.14100](https://doi.org/10.1111/hae.14100)

**IMPORTANT NOTE:** You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

*Document Version*  
Publisher's PDF, also known as Version of record

*Publication date:*  
2020

[Link to publication in University of Groningen/UMCG research database](#)

### *Citation for published version (APA):*

Jonker, C. J., Oude Rengerink, K., Hoes, A. W., Mol, P. G. M., & van den Berg, H. M. (2020). Inhibitor development in previously untreated patients with severe haemophilia: A comparison of included patients and outcomes between a clinical study and a registry-based study. *Haemophilia*, 26(5), 809-816. <https://doi.org/10.1111/hae.14100>

### **Copyright**

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.






### **Take-down policy**

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

*Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.*

## ORIGINAL ARTICLE

# Inhibitor development in previously untreated patients with severe haemophilia: A comparison of included patients and outcomes between a clinical study and a registry-based study

Carla J. Jonker<sup>1,2</sup>  | Katrien Oude Rengerink<sup>1,2</sup>  | Arno W. Hoes<sup>2</sup>  |  
Peter G. M. Mol<sup>1,3</sup>  | H. Marijke van den Berg<sup>4</sup> 

<sup>1</sup>Dutch Medicines Evaluation Board (CBG-MEB), Utrecht, The Netherlands

<sup>2</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, The Netherlands

<sup>3</sup>Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, The Netherlands

<sup>4</sup>PedNet Haemophilia Research foundation, Baarn, The Netherlands

## Correspondence

Carla J. Jonker, Medicines Evaluation Board, Graadt van Roggenweg 500, 3531 AH Utrecht, The Netherlands.  
Emails: c.jonker@cbg-meb.nl;  
c.j.jonker-2@umcutrecht.nl

## Abstract

**Aim:** The aim of this study was to investigate whether a disease registry could serve as a suitable alternative to clinical studies to investigate safety of orphan drugs in children.

**Methods:** We used individual patient data from previously untreated patients (PUPs) with severe haemophilia A from the factor VIII (rAHF-PFM)-clinical study and the PedNet registry. The primary outcome was the patient characteristics at entry and the difference in inhibitor development between the clinical study and the registry-based study at 50 exposure days.

**Results:** Clinical study patients more often had a positive family history of inhibitors (31% vs 10%) and a high-risk F8 genotype (82% vs 63%). In the clinical study 41/55 (75%) and in the registry-based study 162/168 (96%) patients reached 50 exposure days. Inhibitors developed in 16 of the 41 patients in the clinical study (39%) vs 44 of the 162 patients in the registry-based study (27%); seven patients (7%) vs 28 patients (17%) had high-titre inhibitors. The risk of developing an inhibitor during the first 50 exposure days was similar (HR 1.04; 95% CI 0.56-1.94), when adjusted for family history of inhibitors, F8 gene mutation and intensive treatment at first exposure.

**Conclusion:** In the registry-based study, patient numbers and completeness of follow-up were higher. The risk of developing an inhibitor to a single product was comparable. Although the sample size of this study was too small to conclude on differences in high- or low-titre inhibitors, this suggests that a registry could serve as a more suitable source for evaluation of high-titre inhibitors in the setting of factor VIII deficiency.

## KEYWORDS

factor VIII, haemophilia A, inhibitor development, previously untreated patients, registry

## 1 | INTRODUCTION

In the field of orphan diseases, clinical trials are inherently small and relatively often use non-randomized study designs.<sup>1,2</sup> Disease registries may be a reasonable alternative for small, single-arm clinical studies to evaluate safety and efficacy of a drug. A great benefit of registries is that they include 'real-life' patients, and are suited for monitoring safety and beneficial effects over a longer period.<sup>3</sup> Within the regulatory field, the Patient Registry Initiative of the European Medicine Agency is exploring the use of patient registries. This initiative supports a systematic approach for a better use of registry data for the benefit-risk evaluation of medicines, mostly post-marketing.<sup>4,5</sup> To retrieve high-quality registry data, key aspects are a comprehensive enrolment of patients, avoidance of selection bias, collection of essential core data and completeness of data.<sup>5</sup>

Haemophilia A is a rare disease, with a prevalence of 1:5000 new-born males, for which single-arm clinical studies have supported market approval of (recombinant) clotting factors that replace the deficient factor VIII.<sup>6</sup> In various registries, patients with haemophilia are closely monitored for the occurrence of antibodies against administered clotting factor, so-called 'inhibitors'. The occurrence of inhibitor development in previously untreated patients (PUPs) has been reported to be as high as 25%-35%.<sup>7,8</sup> There is an ongoing debate as to whether plasma products might be associated with a lower risk of inhibitor development in comparison with recombinant products.<sup>7,9,10</sup> Different inhibitor incidences between individual recombinant products have also been published.<sup>7-9,11</sup> Major limitations to the interpretation of results from previous clinical studies were due to differences in study design, patient selection and a short follow-up.<sup>12</sup> Recently, data from historic clinical studies were investigated. These data proved unsuitable for comparing immunogenicity between products, due to differences in study design, diversity in enrolled patient populations and small numbers of included patients.<sup>13</sup> Lately, a number of new factor VIII products have been licensed, and many new products are being developed.<sup>14</sup> To investigate the occurrence of inhibitor development for these products, it might be difficult to recruit sufficient PUPs in clinical studies in an appropriate time frame. This knowledge has recently led to a change in the guideline for the investigation of factor VIII products. To retrieve long-term safety data in PUPs, core data elements should be collected in patient registries rather than in small clinical trials.<sup>6</sup>

To investigate whether a registry-based study could serve as a reasonable alternative for a single-arm clinical study, we evaluated inhibitor development in PUPs with severe haemophilia A using the same recombinant FVIII product in a clinical study and a registry-based study. We selected the factor VIII (rAHF-PFM)-clinical study, because the study was performed in the same time frame as the data collected in cohort I of the PedNet registry.

## 2 | METHODS

### 2.1 | Study design

In previously untreated patients (PUPs) with severe haemophilia A using factor VIII (rAHF-PFM), we compared the development of anti-factor VIII antibodies (inhibitors), using individual patient data from the factor VIII (rAHF-PFM) PUP-clinical study and the PedNet registry. We checked all core data elements required in the guideline for regulatory PUP studies, and compared core data elements relevant for patient characteristics and inhibitor formation in the two study populations.

### 2.2 | Data sources

#### 2.2.1 | The clinical study: factor VIII (rAHF-PFM) PUP-clinical study

The factor VIII (rAHF-PFM) clinical study was a prospective clinical study including 55 patients treated with human recombinant FVIII octocog alfa from 24 haemophilia centres ([www.clinicaltrials.gov](http://www.clinicaltrials.gov) trial no: NCT00157157).<sup>15</sup> The participants in this clinical study received a specific intervention (human recombinant FVIII octocog alfa) according to the protocol created by Takeda. The first patient entered the study on 1 April 2004, and the last patient exited on 11 September 2009. Takeda provided the individual patient data of this clinical study to us after they had been fully anonymized.

In line with the definition used in the PedNet study, patients that received 1-4 infusions of rAHF-PFM before entering the study were defined as previously untreated patients (PUPs).

#### 2.2.2 | The registry-based study: PedNet Haemophilia Registry

As of January 2018, the PedNet Haemophilia Registry had included 1035 patients with severe haemophilia A (factor VIII activity at baseline percentage  $\leq 1\%$ ) from 31 haemophilia centres ([www.pednet.eu](http://www.pednet.eu), [www.clinicaltrials.gov](http://www.clinicaltrials.gov) trial no: NCT02979119).<sup>16,17</sup> To provide a contemporaneous comparison to the clinical study, we selected all PUPs treated with human recombinant FVIII octocog alfa who were born between 2000 and 2009. Participants included in the registry received the intervention (human recombinant FVIII octocog alfa) as part of their routine medical care according to the protocol created by PedNet. For this analysis, we used the follow-up data available in January 2018. Sixty-one PedNet patients were selected from six centres that also participated in the clinical study. Due to privacy regulations, we obviously did not have access to, for example initials or date of birth to verify whether a patient was included both in the clinical study and in the registry. We matched patients on the factors F8 genotype mutation (yes/no), family history of inhibitors (yes/

no) and treatment intensity (yes/no). In total, 70 ( $2 \times 35$ ) matched patients matched on these three factors. Importantly, 35 matched patients from the PedNet registry were from centres that did not participate in the clinical study. Thus, this excludes the possibility of an overlap of patients from the clinical study and the PedNet registry.

### 2.3 | Data

We extracted core data elements of the PUP populations from the clinical study and the registry as listed in the guideline.<sup>6</sup> For this study we selected the key patient characteristics of age, gender, type of haemophilia, severity of haemophilia (<1% factor VIII activity), family history of haemophilia (yes/no), family history of inhibitor development (yes/no), product, F8 gene mutation (high risk/low risk) and intensity of treatment at first exposure (yes/no). A high-risk F8 gene mutation was defined as genotypes with large deletions, non-sense mutations and intron inversions. A low-risk F8 gene mutation was defined as genotypes with small deletions and insertions, mis-sense mutations, and splice-site mutations.<sup>15,17</sup> Intense treatment at first exposure was defined as an episode of treatment with factor VIII for a bleed or surgery on at least five consecutive days.

In addition, we collected the duration of treatment (number of exposure days and calendar days) and the number of patients followed until exposure days 20 and 50.

### 2.4 | Outcome parameter

The primary outcome was the percentage of patients developing clinically relevant inhibitors to factor VIII (rAHF-PFM) up to 20 and up to 50 exposure days. A clinically relevant inhibitor is defined as at least two independent positive inhibitor tests with decreased in vivo recovery of factor VIII levels. For the registry laboratory, results are used from the individual laboratories (according to the used inhibitor assay and their cut-off level)<sup>17</sup> and from a central laboratory for the clinical study.<sup>15</sup> High-titre inhibitor was defined as a peak inhibitor titre of at least 5 Bethesda units per millilitre. Testing was performed at least every five exposure days during the first 20 exposure days and thereafter at least every 3 months until 50 exposure days were reached.

The secondary outcome was time to (high/low) inhibitor development defined as the number of exposure days prior to the first positive inhibitor test. An exposure day was defined as a day with one or more infusions of factor VIII.

### 2.5 | Analyses

We used descriptive statistics and chi-square tests to compare the patient characteristics of the PUP populations in the clinical study

and the registry-based study. Using logistic regression, we compared the percentage of patients developing an inhibitor up to 20 and 50 exposure days (ED20 and ED50) unadjusted and adjusted for potential confounders. In this study, we adjusted for family history of inhibitor development (yes/no), F8 gene mutation (high risk/low risk) and intensive treatment at first exposure (yes/no). We performed complete case analysis.

The time to inhibitor development was visualized with a Kaplan-Meier plot, censored at 50 exposure days. Cox regression was used to calculate crude and adjusted hazard ratios for inhibitor development, using the same potential confounders as in the logistic regression analysis. To make the groups comparable for the exposure, subjects were censored at 50 exposure days and subjects, who did not reach 50 exposures days, were censored at their last documented exposure day.

## 3 | RESULTS

### 3.1 | Patients

In the clinical study 55 PUPs and in the registry-based study 168 PUPs with severe haemophilia A were included. Core data elements were available in line with the EMA guideline.<sup>6</sup> The most important patient characteristics that must be documented were included in the clinical study and the registry-based study and are shown in Table 1. All patients were male and used the same recombinant factor VIII product rAHF-PFM during all exposure days. In the clinical study, 17/55 (31%) patients had a positive family history of inhibitors vs 16/168 (10%) in the registry. The number of patients with a high-risk F8 gene mutation in the clinical study was 45/55 (82%) vs 105/168 (63%) in the registry-based study. In the clinical study 8/55 (15%) and in the registry-based study 29/168 (17%) patients received intensive treatment at first exposure.

### 3.2 | Treatment period

In the clinical study 48 (87%) and in the registry-based study 164 (98%) patients received 20 exposure days, or developed an inhibitor within that period. Forty-one (75%) patients in the clinical study and 162 (96%) in the registry-based study reached 50 exposure days or developed an inhibitor (Figure 1 and Table 2).

### 3.3 | Inhibitor development

In the clinical study 11 out of 48 patients (23%) and in the registry-based study 37 out of 164 patients (23%) developed inhibitory antibodies within 20 exposure days (OR 1.02 [95% CI 0.47-2.20]). When adjusted for family history of inhibitors, F8 genotype and treatment intensity the odds ratio was 0.56 (95% CI 0.22-1.43).

TABLE 1 Patient characteristics

Characteristic	Factor VIII (rAHF-PFM) PUP-clinical study (N = 55)	PedNet registry-based study (N = 168)
Previous untreated patient <sup>a</sup> (PUP)	55 (100%)	168 (100%)
Factor VIII activity at baseline		
≤1%	53 (96%)	168 (100%)
>1 and <2%	1 (2%)	0
>2%	1 (2%)	0
Age at first exposure (mo, median, IQR)	9.0 (3.0-11.0) <sup>b</sup>	9.9 (5.3-13.6)
Family history of haemophilia		
Yes	NA	88 (52%)
No	NA	79 (47%)
Unknown	55 (100%)	1 (1%)
Family history of inhibitors		
Yes	17 (31%)	16 (10%)
No	35 (64%)	140 (83%)
Unknown	3 (5%)	12 (7%)
F8 genotype		
High-risk	45 (82%)	105 (63%)
Low-risk	10 (18%)	56 (33%)
Unknown	0	7 (4%)
Intensive treatment on first exposure days for ≥5 d		
Yes	8 (15%)	29 (17%)
No	47 (85%)	139 (83%)

Note: Patient characteristics for patients from the clinical study and the registry-based study, using the same rFVIII product.

<sup>a</sup>In the factor VIII (rAHF-PFM) PUP-clinical study, MTPs were defined as patients using the same recombinant FVIII product before the start of the clinical study; in this study, we defined MTPs as patients that received any exposure of another product before entering the study for rAHF-PFM.

<sup>b</sup>Age is defined in months at time of baseline (clinical study).

In total, 60 patients developed inhibitory antibodies within the first 50 exposure days: in the clinical study 16 out of 41 (39%) and in the registry 44 out of 162 (27%). The odds ratio was 1.72 (95% CI 0.84-3.51). When adjusted for family history of inhibitors, F8 genotype and treatment intensity, the odds ratio was 1.22 (95% CI 0.54-2.75). In the clinical study, 7/41 (17%) patients developed a high-titre of antibodies while in the registry-based study, this occurred in 28 of 162 patients (17%). Patients developed inhibitor antibodies after a median of 15 exposure days in the clinical study (Q1-Q3 10-22 EDs) and in the registry-based study after 14 exposure days (Q1-Q3 10-17 EDs; Table 2). The time between first exposure day and inhibitor development was 5.5 months in the clinical study (Q1-Q3 3.5-10.3), and in the registry-based study, it was 3.1 months (Q1-Q3 1.4-7.9).

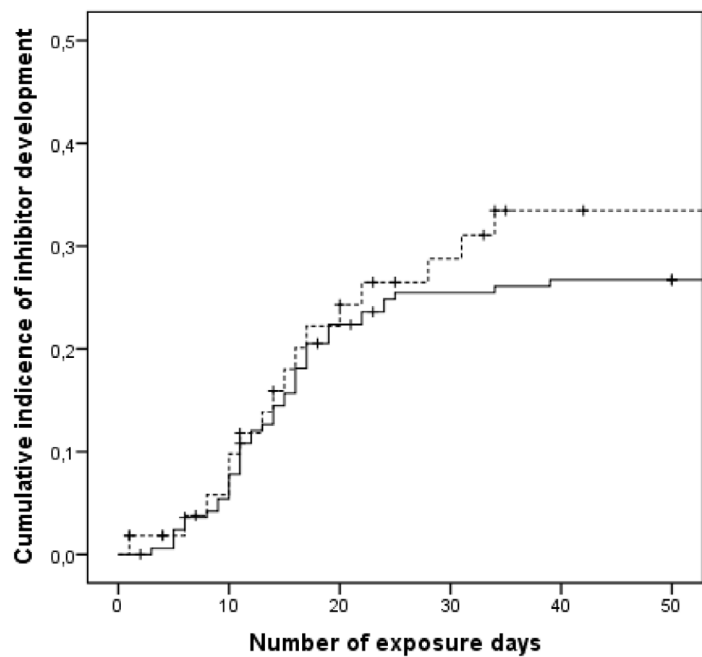
The Kaplan-Meier graph shows the number of exposure days to inhibitor development (Figure 1). We did not observe any differences in inhibitor incidences of patients during the first 20 exposure days. However, after 20 exposure days, the risk to develop an inhibitor was higher for patients in the clinical study.

When using Cox regression analysis, the hazard ratio for inhibitor development was 1.52 (95% CI 0.86-2.69) for patients in the clinical study compared to those in the registry-based study. After adjusting for family history of inhibitors, treatment intensity and F8 genotype, the hazard ratio was 1.04 (95% CI 0.56-1.94).

## 4 | DISCUSSION

At study entry, patient characteristics were different between the clinical study and the registry-based study. In the clinical study, the prevalence of family history of inhibitors was higher and more patients had a high-risk gene mutation. In the clinical study, only 75% of the 55 patients reached 50 exposure days. The follow-up in the registry-based study was more complete with 96% of all 168 patients reaching 50 exposure days. In the clinical study, more patients developed an inhibitor; however, the percentage of patients that developed a high-titre inhibitor was comparable. The risk of developing an inhibitor during the first 50 exposure days was similar

**FIGURE 1** Kaplan-Meier curve for inhibitor development. Kaplan-Meier curves for inhibitor development in PUPs from a clinical study (broken line) and from a registry-based study (solid line). The table below indicates patients numbers with inhibitor development and the patient numbers on treatment at the corresponding exposure days. Patients not followed up to 50 exposure days are right censored.



Patients with inhibitor development	0	10	20	30	40	50
Clinical study	0	3	11	14	16	16
Registry-based study	0	9	37	42	44	44
Patients at risk	0	10	20	30	40	50
Clinical study	55	47	37	31	26	25
Registry-based study	168	157	127	120	118	118

(HR 1.04; 95% CI 0.56-1.94), when adjusted for the main potential confounders.

This is, as far as we know, the first direct comparison of inhibitor development in PUPs, either participating in a clinical study or followed in a registry. Patients in both data sets were treated during the same time period, between 2000 and 2009, and used the same recombinant factor VIII product. Both in the clinical study and in the PedNet registry, the core data elements collected were in line with the guideline.<sup>6</sup> Patients in the registry-based study were followed until January 2018, which led to a higher number of patients reaching 50 exposure days (96%), while this was only 75% for the clinical study. In a systematic review evaluating the incidence of inhibitor development in 24 published clinical studies in PUPs, only in 10 studies was the duration of the treatment longer than 50 exposure days.<sup>18</sup> In registries, the follow-up of patients is mostly longer, with >90% of the patients followed for more than 50 exposure days.<sup>8,11</sup> In the PedNet registry, patients were followed for up to 1000 exposure days. Recently published data

showed that 79% of all inhibitors developed within 20 exposure days and 18% between 20 and 50 exposure days.<sup>16</sup>

In the light of the discussion for the difference in risk rate for plasma and recombinant products, it is interesting that the inhibitor incidence found in both our data sets with a single recombinant FVIII product was similar to that reported for the plasma products in the SIPPET study.<sup>10</sup> It should be acknowledged though that small numbers and selection of patients are important factors that may have influenced the results reported here. Summary statistics of clinical studies have been published via meta-analyses and systemic reviews, comparing inhibitor rates.<sup>12</sup> The contribution of this paper is that we provide a direct comparison of individual data of a published clinical study and compare that to a study embedded in a disease registry. The completeness of the data illustrates that in the field of haemophilia, a well-defined prospective registry could serve as a good data source to study long-term (safety) data of, for example factor VIII products.

Outcome	Factor VIII (rAHF-PFM) PUP-clinical study (N = 55)	PedNet registry-based study (N = 168)
Number of patients (number, %)		
At ED20 <sup>a</sup>	48 (87%)	164 (98%)
At ED50	41 (75%)	162 (96%)
Number of ED at inhibitor development (median, Q1-Q3)		
All	15 (10-22)	14 (10-17)
High-titre	13 (8-16)	14 (10-17)
Number of patients with inhibitor development (number, %) <sup>b</sup>		
At ED20	11 (23%)	37 (23%)
At ED50	16 (39%)	44 (27%)
Number of patients with inhibitor development <sup>c</sup> (number, %)		
Low-titre	9 (22%)	16 (10%)
High-titre	7 (17%)	28 (17%)
Time between first exposure day and inhibitor development (mo, median, Q1-Q3)	5.5 (3.5-10.3)	3.1 (1.4-7.9)

Note: <sup>a</sup>Exposure Day (ED) is defined as a calendar day during which one or more infusions were given; for the clinical study, exposure prior to the start of clinical study was factored into the calculation of the exposure days.

<sup>b</sup>The percentage of inhibitor development up to ED20 or ED50. The percentage is the number of patients with an inhibitor divided by the number of patients that reached ED20 or ED50.

<sup>c</sup> Inhibitor development up to ED50: All inhibitor: defined as the occurrence of at least two positive inhibitor titres combined with a decreased factor VIII recovery; High-titre inhibitor: defined as a peak inhibitor titre of at least 5 Bethesda units per millilitre. The percentage is the number of patients with an inhibitor divided by the number of patients that reached ED50.

**TABLE 2** Duration of treatment and inhibitor development in the Factor VIII (rAHF-PFM) PUP-clinical and the PedNet registry-based study

An issue of clinical studies is the difficulty of recruiting PUPs with severe haemophilia A. In full cohorts such as FranceCoag Network, UKHCDO National Haemophilia Database and PedNet, more than 50% of the patients were diagnosed with a negative family history.<sup>7,8,11</sup> These patients are diagnosed after the onset of bleeding and therefore excluded from clinical studies. In unselected cohorts, only 10% of the patients had a positive family history of inhibitors<sup>19,20</sup> and about 60% of the patients had a high-risk F8 genotype.<sup>21</sup> In the clinical study, more patients had a positive family history of inhibitors and a high-risk F8 genotype; this might have increased the a priori risk of inhibitor development and reduces extrapolation to the general population.<sup>22</sup> The patient characteristics within the registry-based study seem to be more representative of 'real-life' patients from the described full cohorts above.

A limitation of this paper is that we compared data from only one clinical study and one registry-based study. We selected this clinical study because the number of patients included in that study was larger than other PUP studies and factor VIII (rAHF-PFM) is widely used daily clinical practice and in patients included in PedNet. Further comparisons between different concentrates and different study and registry populations may strengthen our conclusions. Obviously, issues on study design, such as, duration of follow-up and inter-laboratory variations, may affect observed inhibitor formation. We, however,

strongly believe that high-titre inhibitors will usually be diagnosed accurately and that registries could substitute for clinical trials in the case of high-titre inhibitors. Despite the sample size of this study was too small to conclude on this, therefore using similar data standards, adhering to those standards and publishing these standards will make data more readily exchangeable between registry (and clinical) studies. In line with McGettigan et al, we think that the value of registries can be increased by clearly described operational proposals on patient registry data, quality assurance processes, governance and stakeholder communication.<sup>5</sup> This study thus illustrates that in the clinical study and the registry-based study, the same patient characteristics and outcome parameters were collected, in line with the guideline.<sup>6</sup>

With all the new products that will be marketed, it is crucial that centres collect data on all PUPs with severe haemophilia and share their results.<sup>23</sup> Products can only be compared independently if data collection methodology is similar and includes all potential confounding factors.<sup>23</sup> The most important limitation of observational drug studies is that different products are given to patients with different a priori inhibitor risk.<sup>24</sup> Rather than performing single-arm PUP studies for separate products, a controlled study (thus comparing two products and adjusting for confounders) within a registry would, in our view, be feasible and may be more efficient.<sup>25</sup> We believe that further optimization may be achieved by performing randomized studies within registries.<sup>25</sup>



## 5 | CONCLUSION

Our paper provides an example showing that patient characteristics were slightly different between a clinical study and a registry-based study. In the clinical study, a higher percentage of patients developed an inhibitor. The number of withdrawals was higher in the clinical study; the completeness of the follow-up was better in the registry. This study indicates that registries like PedNet are potentially useful in assessing the inhibitor developments in treatments for haemophilia and may serve as an alternative to uncontrolled clinical studies for evaluation of high-titre inhibitors. Although the sample size of this study was too small to conclude on differences in high- or low-titre inhibitors, this paper contributes to the discussion for the use of registry-based studies to assess long-term safety data.

## ACKNOWLEDGEMENTS

We would like to thank Takeda for providing data from the factor VIII (rAHF-PFM) PUP-clinical study. The authors thank the PedNet group for providing data from the PedNet registry and Ella van Hardeveld for assistance in preparing the analysis files.

## DISCLOSURES

All of the authors state that they have no financial or personal relationships that inappropriately influenced their role in this work. No funds for the content of this manuscript or the preparation of the manuscript were received by any of the authors.

## AUTHOR CONTRIBUTIONS

CJ Jonker wrote the manuscript and analysed the data. K Oude Rengerink, AW Hoes, PGM Mol and HM van den Berg participated in discussions and reviewed the article. All of the authors had full access to the data and participated in the design of the analysis, discussion of results and revising the draft manuscript.

## ORCID

Carla J. Jonker  <https://orcid.org/0000-0002-9093-2893>

Katrien Oude Rengerink  <https://orcid.org/0000-0002-2596-7678>

Arno W. Hoes  <https://orcid.org/0000-0002-8747-6479>

Peter G. M. Mol  <https://orcid.org/0000-0002-4262-3180>

H. Marijke van den Berg  <https://orcid.org/0000-0002-2553-2324>

## REFERENCES

- Kesselheim AS, Myers JA, Avorn J. Characteristics of clinical trials to support approval of orphan vs non-orphan drugs for cancer. *JAMA*. 2011;305(22):2320-2326.
- Bell SA, Tudur SC. A comparison of interventional clinical trials in rare versus non-rare diseases: an analysis of ClinicalTrials.gov. *Orphanet J Rare Dis*. 2014;26(9):170.
- Gooderham M, Papp K. Clinical trial and registry data. *Curr Probl Dermatol*. 2018;53:15-27.
- Olmo CA, McGettigan P, Kurz X. Barriers and opportunities for use of patient registries in medicines regulation. *Clin Pharmacol Ther*. 2019;106(1):39-42.
- McGettigan P, Alonso Olmo C, Plueschke K, et al. Patient registries: an underused resource for medicines evaluation. *Drug Saf*. 2019;42(11):1343-1351.
- Guideline on the clinical investigation of recombinant and human plasma-derived factor VIII products. [https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2\\_en.pdf](https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-clinical-investigation-recombinant-human-plasma-derived-factor-viii-products-revision-2_en.pdf). Accessed June 15, 2020.
- Gouw SC, van der Bom JG, Ljung R, et al. Factor VIII products and inhibitor development in severe hemophilia A. *N Engl J Med*. 2013;368(3):231-239.
- Calvez T, Chambost H, Claeysens-Donadel S, et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A. *Blood*. 2014;124(23):3398-3408.
- Goudemand J, Rothschild C, Demiguel V, et al. Influence of the type of factor VIII concentrate on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A. *Blood*. 2006;107(1):46-51.
- Peyvandi F, Mannucci PM, Garagiola I, et al. A randomized trial of factor VIII and neutralizing antibodies in hemophilia A. *N Engl J Med*. 2016;374(21):2054-2064.
- Collins PW, Palmer BP, Chalmers EA, et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe hemophilia A, 2000-2011. *Blood*. 2014;124(23):3389-3397.
- Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A: a systematic review. *Haemophilia*. 2003;9(4):418-435. Review.
- Keipert C, Jonker CJ, van den Berg HM, Hilger A. Clinical trials and registries in haemophilia: opponents or collaborators? Comparison of PUP data derived from different data sources. *Haemophilia*. 2018;24(3):420-428.
- Weyand AC, Pipe SW. New therapies for hemophilia. *Blood*. 2019;133(5):389-398.
- Auerswald G, Thompson AA, Recht M, et al. Experience of advance rAHF-PFM in previously untreated patients and minimally treated patients with haemophilia A. *Thromb Haemost*. 2012;107(6):1072-1082.
- Van den Berg HM, Fischer K, Carcao M, et al. Timing of inhibitor development in >1000 previously untreated patients with severe haemophilia A. *Blood*. 2019;134(3):317-320.
- Fischer K, Ljung R, Platokouki H, et al. Prospective observational cohort studies for studying rare diseases: the European PedNet Haemophilia Registry. *Haemophilia*. 2014;20(4):e280-e286.
- Iorio A, Halimeh S, Holzhauser S, et al. Rate of inhibitor development in previously untreated hemophilia A patients treated with plasma-derived or recombinant factor VIII concentrates: a systematic review. *J Thromb Haemost*. 2010;8(6):1256-1265.
- Hashemi SM, Fischer K, Moons KG, van den Berg HM. Improved prediction of inhibitor development in previously untreated patients with severe haemophilia A. *Haemophilia*. 2015;21(2):227-233.
- Coppola A, Santoro C, Tagliaferri A, Franchini M, Di Minno G. Understanding inhibitor development in haemophilia A: towards clinical prediction and prevention strategies. *Haemophilia*. 2010;16(Suppl 1):13-19.
- Volkers P, Hanschmann KM, Calvez T, et al. Recombinant factor VIII products and inhibitor development in previously untreated patients with severe haemophilia A: combined analysis of three studies. *Haemophilia*. 2019;25(3):398-407.
- Astermark J, Berntorp E, White GC II, Kroner BL, the MIBS Study Group. The Malmö International Brother Study (MIBS): further





- support for genetic predisposition to inhibitor development in haemophilia patients. *Haemophilia*. 2001;7:267-272.
23. Van den Berg HM. Different impact of factor VIII products on inhibitor development? *Thromb J*. 2016;14(Suppl 1):31.
  24. Iorio A, Fischer K, Makris M. Large scale studies assessing anti-factor VIII antibody development in previously untreated haemophilia A: what has been learned, what to believe and how to learn more. *Br J Haematol*. 2017;178(1):20-31.
  25. Lauer MS, D'Agostino RB Sr. The randomized registry trial—the next disruptive technology in clinical research? *N Engl J Med*. 2013;369(17):1579-1581.

**How to cite this article:** Jonker CJ, Oude Rengerink K, Hoes AW, Mol PGM, van den Berg HM. Inhibitor development in previously untreated patients with severe haemophilia: A comparison of included patients and outcomes between a clinical study and a registry-based study. *Haemophilia*. 2020;00:1–8. <https://doi.org/10.1111/hae.14100>